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EXAMINER	
FORMAN, BETTY J	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/375,248	FERRELL ET AL.
	Examiner	Art Unit
	BJ Forman	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 37-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 37-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). Feb 03
4) ☒ Interview Summary (PTO-413) Paper No(s). May 03
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to papers filed 10 February 2003 in which a Declaration under 37 C.F.R. 1.132 was submitted, claims 1, 7 and 38 were amended, claims 14-21 were canceled and claims 39-48 were added. All of the amendments have been thoroughly reviewed and entered. The previous rejections in the Office Action dated 6 August 2002 under 35 U.S.C. 112, second paragraph are withdrawn in view of the amendments. The previous rejections under 35 U.S.C. 102(a) and 35 U.S.C. 103(a) are withdrawn in view of the amendments and Declaration. All of the arguments have been thoroughly reviewed but are deemed moot in view of the amendments, withdrawn rejections and new grounds for rejection.

New grounds for rejection are discussed.

Claims 1-11 and 37-48 are under prosecution.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

First paragraph of 35 U.S.C. 112: Enablement

3. Claims 1-11 and 37-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to method for assaying risk of developing hereditary lymphedema by assaying the nucleic acid of a human for a mutation in at least one VEGFR-3 allele to thereby correlate the presence or absence of the mutation with an increased or no increased risk of developing hereditary lymphedema.

The specification is enabling for the method wherein the mutations consist of (1) a missence mutation at nucleotide 3360 of SEQ ID NO: 1, causing a proline to leucine change at residue 1 1 14 in SEQ ID NO: 2,. (2) a missense mutation at nucleotide 2588 of SEQ ID NO: 1, causing a glycine to arginine change at residue 857 in SEQ ID NO: 2, (3) a missense mutation at nucleotide 3 141 of SEQ ID NO: 1, causing an arginine to proline change at residue 1041 in SEQ ID NO: 2, (4) a missence mutation at nucleotide 3150 in SEQ ID NO: 1, causing a leucine to proline change at residue 1044 in SEQ ID NO: 2, and (5) a missence mutation at nucleotide 3 164 of SEQ ID NO: 1, causing an aspartic acid to asparagine change at residue 1049 in SEQ ID NO: 2."

However, the specification does not enable one skilled in the art to which it pertains or with which it is most nearly connected to make or use the invention commensurate in scope with the claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to:

Breadth of the Claims

The claims are broadly drawn to method for assaying risk of developing hereditary lymphedema by assaying the nucleic acid of a human for a mutation in at least one VEGFR-3 allele to thereby correlate the presence or absence of the mutation with an increased or no increased risk of developing hereditary lymphedema.

The claims are written so broadly so as to encompass any type of mutation including mismatch, missense, deletion, translocation, inversion, substitution, single nucleotide polymorphism, conditional mutation, loss-of-function and gain-of-function. However, the specification merely teaches (1) a missense mutation at nucleotide 3360 of SEQ ID NO: 1, causing a proline to leucine change at residue 1 1 14 in SEQ ID NO: 2,. (2) a missense mutation at nucleotide 2588 of SEQ ID NO: 1, causing a glycine to arginine change at residue 857 in SEQ ID NO: 2, (3) a missense mutation at nucleotide 3 141 of SEQ ID NO: 1, causing an arginine to proline change at residue 1041 in SEQ ID NO: 2, (4) a missence mutation at nucleotide 3150 in SEQ ID NO: 1, causing a leucine to proline change at residue 1044 in SEQ ID NO: 2, and (5) a missence mutation at nucleotide 3 164 of SEQ ID NO: 1, causing an aspartic acid to asparagine change at residue 1049 in SEQ ID NO: 2." (page 11).

The claims are written so broadly so as to encompass any VEGFR-3 allele. However, the specification merely teaches a missense mutation in the VEGFR-3 gene (which maps to chromosome 5q34-q35) exists that appears to behave in a loss-of-function dominant (page 4, lines 19-20).

The claims (Claims 3-4) are written so broadly so as to encompass any missense mutation "corresponding" to codons 857, 1041, 1044, 1049 and 1114 which includes mutations in any one of the three nucleotides within the codons and further includes mutations which correspond positionally, functionally, structurally and/or some other non-

described manner to the codons. However, the specification merely teaches 5 missense mutations which are positioned within the codons.

While the specification is enabling for the method for determining an increased risk for developing hereditary lymphedema, the specification is not enabling for the broadly claimed invention.

Nature of the Invention

The claims are drawn to methods for assaying a risk of developing hereditary lymphedema comprising steps of assaying the nucleic acid of a human for a mutation in at least one VEGFR-3 allele and correlating the presence or absence of the mutation with an increased or no increased risk of developing hereditary lymphedema.

The nature of the invention is such that assaying for the risk of a disease would require a teaching of a relationship between the method steps and disease risk wherein the teaching would minimally include an illustration or examples of the relationship between the broadly claimed mutations and the risk/no risk for developing hereditary lymphedema. The specification does not provide a teaching of the relationship between the broadly claimed mutations and the risk/no risk for developing hereditary lymphedema.

The specification teaches that a relationship exists between 5 missense mutations and an increased risk for developing hereditary lymphedema (page 11). The specification also teaches methods for assaying for the 5 mutations thereby illustrating the relationship between the 5 missense mutations and hereditary lymphedema. However, the specification does not teach a relationship between the broadly claimed mutations and an increased or no increased risk for developing hereditary lymphedema would enable one of skill in the art to make and use

the invention as claimed. Therefore, the specification, in view of the nature of the invention, does not enable the instantly claimed invention.

State of the Prior Art

The claims are drawn to methods for assaying a risk of developing hereditary lymphedema comprising steps of assaying the nucleic acid of a human for a mutation in at least one VEGFR-3 allele and correlating the presence or absence of the mutation with an increased or no increased risk of developing hereditary lymphedema.

The state of the prior art is such that processes for detecting the presence or absence of mutations were known. Furthermore, it was known in the art that mutations in the VEGFR-3 gene alter signaling by the VEGFR-3 encoded protein as taught by Fournier et al (Oncogene, 1995, 11: 921-931). Fournier et al further teach that the VEGFR-3 is expressed in a wide variety of tissues (page 928, Table 2) suggesting that VEGFR-3 protein signaling provides a variety of functions.

Therefore, the prior art of record does not teach that the instantly claimed method of assaying for a mutation in at least one allele of the VEGFR-3 gene would assay the risk of developing hereditary lymphedema as instantly claimed.

Therefore, neither the specification nor the prior art of record teach a relationship between the broadly claimed VEGFR-3 mutations and an increased risk or no increased risk for developing hereditary lymphedema which would enable one of skill in the art to make and use the invention as claimed.

Level of Predictability in the Art

The claims are drawn to methods for assaying a risk of developing hereditary lymphedema comprising steps of assaying the nucleic acid of a human for a mutation in at least one VEGFR-3 allele and correlating the presence or absence of the mutation with an increased or no increased risk of developing hereditary lymphedema.

The level of predictability in the art is very low regarding detecting any mutation in a gene and from that detection determines the risk for disease. The claims are drawn to assaying for a mutation in the VEGFR-3 gene which encompasses a wide variety of mutations and the encoded amino acid sequence resulting from the mutations would encompass a very large genus of proteins. The certainty that any one of the proteins within the very large genus of proteins would determine the risk for disease would be very low.

Therefore the predictability that the broadly claimed invention would determine risk of developing hereditary lymphedema would also be very low. Because the level of predictability regarding mutation detection and risk determination would be very low, and because the specification merely teaches characterization of 5 mutations predictive of risk, the specification does not enable one of skill in the art to make and use the invention as claimed.

Existence of Working Examples

The claims are drawn to methods for assaying a risk of developing hereditary lymphedema comprising steps of assaying the nucleic acid of a human for a mutation in at least one VEGFR-3 allele and correlating the presence or absence of the mutation with an increased or no increased risk of developing hereditary lymphedema.

The specification characterizes 5 missense mutations present in individuals having the disease (page 11) and the specification teaches methods for assaying for the presence of 5 missense mutations to thereby determine an increased risk for developing hereditary lymphedema (Example 1).

The specification does not teach working examples of the broadly claimed invention whereby assaying for any mutation in at least one VEGFR-3 allele determines an increased risk or no risk for developing hereditary lymphedema. Therefore, the specification does not provide working examples of the broadly claimed invention which would enable one of ordinary skill in the art to make and use the invention as claimed.

Quantity of Experimentation Required

The claims are drawn to methods for assaying a risk of developing hereditary lymphedema comprising steps of assaying the nucleic acid of a human for a mutation in at least one VEGFR-3 allele and correlating the presence or absence of the mutation with an increased or no increased risk of developing hereditary lymphedema.

In view of the breadth of the claims being drawn to encompass any type of mutation, any VEGFR-3 allele, and any missense mutation "corresponding" to codons 857, 1041, 1044, 1049 and 1114; in view of the nature of the invention in which assaying for the risk of a disease would require a teaching of a relationship between the method steps (i.e. mutation detection) and disease risk and the lack of a teaching in the specification of the required relationship; in view of the state of the prior art wherein it is taught that VEGFR-3 is expressed in a wide variety of tissues (page 928, Table 2) suggesting that VEGFR-3 protein signaling provides a variety of functions; in view of the of unpredictability in the art with regard to mutation detection and disease risk; and in view of the lack of working examples of the broadly

claimed invention, it would require undue experimentation for one skilled in the art to make and use the invention as claimed.

First paragraph of 35 U.S.C. 112: Written Description

4. Claims 1-11 and 37-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to methods of assaying for a risk of developing hereditary lymphedema comprising assaying a nucleic acid sample for a mutation that alters the encoded amino acid sequence of at least one VEGFR-3 allele. However, the specification does not provide and adequate written description of the claimed invention. The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Reduction to practice

The specification does not describe an actual reduction to practice of the broadly claimed invention. The claims are broadly drawn to method for assaying risk of developing hereditary lymphedema by assaying the nucleic acid of a human for a mutation in at least one VEGFR-3 allele. The specification teaches "several mutations that have been characterized herein in affected individuals, including: (1) a essence mutation at nucleotide 3360 of SEQ ID NO: 1, causing a proline to leucine change at residue 1 1 14 in SEQ ID NO: 2,. (2) a masseuse mutation at nucleotide 2588 of SEQ ID NO: 1, causing a glycine to arginine change at residue 857 in SEQ ID NO: 2, (3) a masseuse mutation at nucleotide 3 141 of SEQ ID NO: 1, causing an arginine to proline change at residue 1041 in SEQ ID NO: 2, (4) a essence mutation at nucleotide 3150 in SEQ ID NO: 1, causing a leucine to proline change at residue 1044 in SEQ ID NO: 2, and (5) a essence mutation at nucleotide 3 164 of SEQ ID NO: 1, causing an aspartic acid to asparagine change at residue 1049 in SEQ ID NO: 2." (page 11). While the specification teaches the above listed mutations correlate with an increased risk of developing hereditary lymphedema and the specification teaches assaying for the above mutations, the specification does not reduce to practice the detection of any mutation in any allele determines an increased risk or no increased risk of developing hereditary lymphedema as broadly claimed. Therefore, the specification does not describe an actual reduction to practice of the broadly claimed method.

Completed by drawings

The specification does not teach that the invention is complete as evidenced by drawings. The claims are broadly drawn to method for assaying risk of developing hereditary lymphedema by assaying the nucleic acid of a human for a mutation in at least one VEGFR-3 allele. The drawings of the specification illustrate the linkage analysis for hereditary lymphedema (Fig. 1); genomic mapping of the VEGFR-3 gene (Fig.2); and amino acid alignment of the human and mouse VEGFR-3 gene (Fig. 3).

However, the drawings do not provide evidence that the invention is complete because the drawings do not provide or complete the description of the method for assaying for a mutation in at least one VEGFR-3 allele to thereby determine the risk of developing hereditary lymphedema.

Description of identifying characteristics

The specification has not been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention. The specification teaches "several mutations that have been characterized herein in affected individuals, including: (1) a missence mutation at nucleotide 3360 of SEQ ID NO: 1, causing a proline to leucine change at residue 1 1 14 in SEQ ID NO: 2,. (2) a missense mutation at nucleotide 2588 of SEQ ID NO: 1, causing a glycine to arginine change at residue 857 in SEQ ID NO: 2, (3) a missense mutation at nucleotide 3 141 of SEQ ID NO: 1, causing an arginine to proline change at residue 1041 in SEQ ID NO: 2, (4) a missence mutation at nucleotide 3150 in SEQ ID NO: 1, causing a leucine to proline change at residue 1044 in SEQ ID NO: 2, and (5) a missence mutation at nucleotide 3 164 of SEQ ID NO: 1, causing an aspartic acid to asparagine change at residue 1049 in SEQ ID NO: 2." (page 11). The specification has not described identifying characteristics of more than one VEGFR-3 allele as instantly claimed; the specification has not described identifying characteristics reduced signaling of the VEGRF-3 allele; the specification has not described identifying characteristics of a positions "corresponding to" codons 857,1041,1044, 0149 and 1114 (other than the missense mutations listed above) as instantly claimed; the specification has not described identifying characteristics of mutations (other than those listed above) which correlate with increased risk as instantly claimed; the specification has not described identifying characteristics which correlate with no increased risk as instantly claimed. Therefore, the specification doe not teach or describe identifying characteristics which show that applicant was in possession of the broadly claimed method.

Therefore, the specification does not provide a written description of the claimed invention in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The courts have stated that the specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonable conclude the inventor had possession of the claimed invention see *In re Vas-Cath*, Inc. 935F2d. 1555, 1563, 19 USPQ2d 1111,1116

Second paragraph of 35 U.S.C. 112: Indefinite

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

c. Claims 3 and 4 are each indefinite for the recitation "assaying for a missense mutation in a VEGFR-3 allele at a position corresponding to one of codons...." Because "corresponding" is a non-specific relational term and therefore it is unclear whether the assaying detects a mutation within one of the codons or at some position which merely corresponds to one of the codons in an undefined manner. As such, the relationship between the mutation and the codons is undefined. It is suggested that Claims 3 and 4 both be

amended to clarify (e.g. recite the specific mutations identified in the specification at page 11 which define the invention).

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The claims are drawn to methods of assaying for risk of lymphedema comprising assaying the nucleic acid of a human for a mutation that "reduces" ligand mediated signaling wherein the presence of the mutation "correlates" with an increased risk of lymphedema. The claims do not recite method steps of measuring ligand mediated signaling; the claims do not define "reduced" signaling; the claims do not define the correlation between mutations and increased risk; the claims do not define the correlation between mutations and no increased risk. The claims are given the broadest reasonable interpretation consistent with the broad and indefinite claim language.

The courts have stated that claims must be given their broadest reasonable interpretation consistent with the specification *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969); and *In re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) (see MPEP 2111).

8. Claims 1, 2, 4-10, 37-40 and 42-47 are rejected under 35 U.S.C. 102(a) as being anticipated by Lawrence et al (The American Journal of Human Genetics, October 1998, 63(4), A185, Abstract 1053).

Regarding Claim 1, Lawrence et al disclose a method of assaying for risk of developing hereditary lymphedema comprising: assaying nucleic acid of a human subject for a mutation altering the encoded amino acid sequence of at least one VEGFR-3 allele in a manner that reduces ligand-mediated signaling of the VEGFR-3 polypeptide and correlating the presence or absence of said mutation to a risk of developing hereditary lymphedema wherein presence of said mutation correlates with an increased risk of and absence of said mutation correlates with no increased risk of developing hereditary lymphedema (Abstract). The mutations described by Lawrence et al are correlated with increased risk with lymphedema as claimed. While Lawrence et al do not recite method steps of measuring ligand mediated signaling, the claims do not require the measurement or define "reduced". As such, Lawrence et al disclose the method as claimed.

Regarding Claim 2, Lawrence et al disclose the method wherein the assaying step comprises assaying for a mutation (Abstract). The mutations described by Lawrence et al are correlated with increased risk with lymphedema as claimed. While Lawrence et al do not recite method steps of determining altered tyrosine kinase domain, the claims do not require the measurement or define "altered". As such, Lawrence et al disclose the method as claimed.

Regarding Claim 4, Lawrence et al disclose the method wherein the assaying step comprises assaying for a missense mutation in a VEGFR-3 allele at a position corresponding to codon 1114 (Abstract).

Regarding Claim 5, Lawrence et al disclose at least one of the known VEFFR-3 mutations is identified by restriction digestion.

Regarding Claim 7, Lawrence et al disclose a method for a VEGFR-3 hereditary lymphedema genotype comprising: providing a biological sample and determining a VEGFR-3

genotype by analyzing the nucleic acid for a mutation altering the encoded amino acid sequence of at least one VEGFR-3 allele in a manner that reduces ligand-mediated signaling of the VEGFR-3 polypeptide and correlating the presence or absence of said mutation to a risk of developing hereditary lymphedema wherein presence of said mutation identifies a hereditary lymphedema genotype (Abstract). The mutations described by Lawrence et al identify hereditary lymphedema as claimed. While Lawrence et al do not recite method steps of measuring peptide mediated signaling, the claims do not require the measurement or define "reduced". As such, Lawrence et al disclose the method as claimed.

Regarding Claim 8, Lawrence et al disclose the method of Claim 7 wherein said biological sample is a cell sample (Abstract).

Regarding Claim 9, Lawrence et al disclose the method of Claim 7 wherein analyzing comprises sequencing a portion of said nucleic acid (Abstract).

Regarding Claim 10, Lawrence et al disclose the method of Claim 7 wherein the nucleic acid is DNA (Abstract).

Regarding Claim 37, Lawrence et al disclose a method of screening a human subject for an increased risk, the method comprising, assaying the nucleic acid of a subject for a mutation that alters the encoded amino acid sequence for at least one VEGFR-3 allele wherein the altered amino acid sequence "correlates" with hereditary lymphedema (Abstract). The claim is broadly drawn to a method comprising a single step of assaying the nucleic acid of a human subject. As such, Lawrence et al disclose the method as claimed.

Regarding Claim 38, Lawrence et al disclose the method wherein said mutation reduces signaling of the VEGFR-3 receptor (Abstract).

Regarding Claim 39, Lawrence et al disclose the method wherein the assaying identifies the presence of the mutation and identifies the increased risk (Abstract).

Regarding Claim 40, Lawrence et al disclose the method of claim 2 wherein the assaying identifies a mutation altering a tyrosine kinase domain amino acid sequence of the

protein encoded by the VEGFR-3 allele.

Regarding Claim 42, Lawrence et al disclose the method of claim 4 wherein the assaying identifies the missense mutation in a VEGFR-3 allele in the human subject.

Regarding Claim 43, Lawrence et al disclose the method of claim 7 wherein the human subject has a hereditary lymphedema genotype identified by the method of screening.

Regarding Claim 44, Lawrence et al disclose the method of Claims 37 or 38 wherein the human subject has a mutation that alters the encoded amino acid sequence of at least one VEGFR-3 allele in a manner that correlates with the risk of developing hereditary lymphedema.

Regarding Claim 45, Lawrence et al disclose the method of claim 1, wherein the wildtype VEGFR-3 allele comprises the VEGFR-3 coding sequence set forth in SEQ ID NO: 1.

Regarding Claim 46, Lawrence et al disclose the method of claim 7, wherein the wildtype VEGFR-3 allele comprises the VEGFR-3 coding sequence set forth in SEQ ID NO: 1.

Regarding Claim 47, Lawrence et al disclose the method of claim 38, wherein the wildtype VEGFR-3 allele comprises the VEGFR-3 coding sequence set forth in SEQ ID NO: 1.

9. Claims 1, 2, 4-10, 37-40 and 42-47 are rejected under 35 U.S.C. 102(a) as being anticipated by Kimak et al (The American Journal of Human Genetics, October 1998, 63(4), A185, Abstract 180).

Regarding Claim 1, Kimak et al disclose a method of assaying for risk of developing hereditary lymphedema comprising: assaying nucleic acid of a human subject for a mutation altering the encoded amino acid sequence of at least one VEGFR-3 allele in a manner that reduces ligand-mediated signaling of the VEGFR-3 polypeptide and correlating the presence or absence of said mutation to a risk of developing hereditary lymphedema wherein presence of

said mutation correlates with an increased risk of and absence of said mutation correlates with no increased risk of developing hereditary lymphedema (Abstract). The mutations described by Kimak et al are correlated with increased risk with lymphedema as claimed. While Kimak et al do not recite method steps of measuring ligand mediated signaling, the claims do not require the measurement or define "reduced". As such, Kimak et al disclose the method as claimed.

Regarding Claim 2, Kimak et al disclose the method wherein the assaying step comprises assaying for a mutation (Abstract). The mutations described by Kimak et al are correlated with increased risk with lymphedema as claimed. While Kimak et al do not recite method steps of determining altered tyrosine kinase domain, the claims do not require the measurement or define "altered". As such, Kimak et al disclose the method as claimed.

Regarding Claim 4, Kimak et al disclose the method wherein the assaying step comprises assaying for a missense mutation in a VEGFR-3 allele at a position corresponding to codon 1114 (Abstract).

Regarding Claim 5, Kimak et al disclose at least one of the known VEFFR-3 mutations is identified by perform sequencing, hybridization, migration assay and restriction digestion (Abstract).

Regarding Claim 7, Kimak et al disclose a method for a VEGFR-3 hereditary lymphedema genotype comprising: providing a biological sample and determining a VEGFR-3 genotype by analyzing the nucleic acid for a mutation altering the encoded amino acid sequence of at least one VEGFR-3 allele in a manner that reduces ligand-mediated signaling of the VEGFR-3 polypeptide and correlating the presence or absence of said mutation to a risk of developing hereditary lymphedema wherein presence of said mutation identifies a hereditary lymphedema genotype (Abstract). The mutations described by Kimak et al identify hereditary lymphedema as claimed. While Kimak et al do not recite method steps of measuring peptide

mediated signaling, the claims do not require the measurement or define "reduced". As such, Kimak et al disclose the method as claimed.

Regarding Claim 8, Kimak et al disclose the method of Claim 7 wherein said biological sample is a cell sample (Abstract).

Regarding Claim 9, Kimak et al disclose the method of Claim 7 wherein analyzing comprises sequencing a portion of said nucleic acid (Abstract).

Regarding Claim 10, Kimak et al disclose the method of Claim 7 wherein the nucleic acid is DNA (Abstract).

Regarding Claim 37, Kimak et al disclose a method of screening a human subject for an increased risk, the method comprising, assaying the nucleic acid of a subject for a mutation that alters the encoded amino acid sequence for at least one VEGFR-3 allele wherein the altered amino acid sequence "correlates" with hereditary lymphedema (Abstract). The claim is broadly drawn to a method comprising a single step of assaying the nucleic acid of a human subject. As such, Kimak et al disclose the method as claimed.

Regarding Claim 38, Kimak et al disclose the method wherein said mutation reduces signaling of the VEGFR-3 receptor (Abstract).

Regarding Claim 39, Kimak et al disclose the method wherein the assaying identifies the presence of the mutation and identifies the increased risk (Abstract).

Regarding Claim 40, Kimak et al disclose the method of claim 2 wherein the assaying identifies a mutation altering a tyrosine kinase domain amino acid sequence of the protein encoded by the VEGFR-3 allele.

Regarding Claim 42, Kimak et al disclose the method of claim 4 wherein the assaying identifies the missense mutation in a VEGFR-3 allele in the human subject.

Regarding Claim 43, Kimak et al disclose the method of claim 7 wherein the human subject has a hereditary lymphedema genotype identified by the method of screening.

Regarding Claim 44, Kimak et al disclose the method of Claims 37 or 38 wherein the human subject has a mutation that alters the encoded amino acid sequence of at least one VEGFR-3 allele in a manner that correlates with the risk of developing hereditary lymphedema.

Regarding Claim 45, Kimak et al disclose the method of claim 1, wherein the wildtype VEGFR-3 allele comprises the VEGFR-3 coding sequence set forth in SEQ ID NO: 1.

Regarding Claim 46, Kimak et al disclose the method of claim 7, wherein the wildtype VEGFR-3 allele comprises the VEGFR-3 coding sequence set forth in SEQ ID NO: 1.

Regarding Claim 47, Kimak et al disclose the method of claim 38, wherein the wildtype VEGFR-3 allele comprises the VEGFR-3 coding sequence set forth in SEQ ID NO: 1.

10. Claims 1, 2, 4-10, 37-40 and 42-47 are rejected under 35 U.S.C. 102(a) as being anticipated by Witte et al (Lymphology, 1998, 31, 145-155).

Regarding Claim 1, Witte et al disclose a method of assaying for risk of developing hereditary lymphedema comprising: assaying nucleic acid of a human subject for a mutation altering the encoded amino acid sequence of at least one VEGFR-3 allele in a manner that reduces ligand-mediated signaling of the VEGFR-3 polypeptide and correlating the presence or absence of said mutation to a risk of developing hereditary lymphedema wherein presence of said mutation correlates with an increased risk of and absence of said mutation correlates with no increased risk of developing hereditary lymphedema (Abstract). The mutations described by Witte et al are correlated with increased risk with lymphedema as claimed. While Witte et al do not recite method steps of measuring ligand mediated signaling, the claims do not require the measurement or define "reduced". As such, Witte et al disclose the method as claimed.

Regarding Claim 2, Witte et al disclose the method wherein the assaying step comprises assaying for a mutation (Abstract). The mutations described by Witte et al are correlated with increased risk with lymphedema as claimed. While Witte et al do not recite method steps of determining altered tyrosine kinase domain, the claims do not require the measurement or define "altered". As such, Witte et al disclose the method as claimed.

Regarding Claim 4, Witte et al disclose the method wherein the assaying step comprises assaying for a missense mutation in a VEGFR-3 allele at a position corresponding to codon 1114 (Abstract).

Regarding Claim 5, Witte et al disclose at least one of the known VEFFR-3 mutations is identified by perform sequencing, hybridization, migration assay and restriction digestion (Abstract).

Regarding Claim 7, Witte et al disclose a method for a VEGFR-3 hereditary lymphedema genotype comprising: providing a biological sample and determining a VEGFR-3 genotype by analyzing the nucleic acid for a mutation altering the encoded amino acid sequence of at least one VEGFR-3 allele in a manner that reduces ligand-mediated signaling of the VEGFR-3 polypeptide and correlating the presence or absence of said mutation to a risk of developing hereditary lymphedema wherein presence of said mutation identifies a hereditary lymphedema genotype (Abstract). The mutations described by Witte et al identify hereditary lymphedema as claimed. While Witte et al do not recite method steps of measuring peptide mediated signaling, the claims do not require the measurement or define "reduced". As such, Witte et al disclose the method as claimed.

Regarding Claim 8, Witte et al disclose the method of Claim 7 wherein said biological sample is a cell sample (Abstract).

Regarding Claim 9, Witte et al disclose the method of Claim 7 wherein analyzing comprises sequencing a portion of said nucleic acid (Abstract).

Regarding Claim 10, Witte et al disclose the method of Claim 7 wherein the nucleic acid is DNA (Abstract).

Regarding Claim 37, Witte et al disclose a method of screening a human subject for an increased risk, the method comprising, assaying the nucleic acid of a subject for a mutation that alters the encoded amino acid sequence for at least one VEGFR-3 allele wherein the altered amino acid sequence "correlates" with hereditary lymphedema (Abstract). The claim is broadly drawn to a method comprising a single step of assaying the nucleic acid of a human subject. As such, Witte et al disclose the method as claimed.

Regarding Claim 38, Witte et al disclose the method wherein said mutation reduces signaling of the VEGFR-3 receptor (Abstract).

Regarding Claim 39, Witte et al disclose the method wherein the assaying identifies the presence of the mutation and identifies the increased risk (Abstract).

Regarding Claim 40, Witte et al disclose the method of claim 2 wherein the assaying identifies a mutation altering a tyrosine kinase domain amino acid sequence of the protein encoded by the VEGFR-3 allele.

Regarding Claim 42, Witte et al disclose the method of claim 4 wherein the assaying identifies the missense mutation in a VEGFR-3 allele in the human subject.

Regarding Claim 43, Witte et al disclose the method of claim 7 wherein the human subject has a hereditary lymphedema genotype identified by the method of screening.

Regarding Claim 44, Witte et al disclose the method of Claims 37 or 38 wherein the human subject has a mutation that alters the encoded amino acid sequence of at least one VEGFR-3 allele in a manner that correlates with the risk of developing hereditary lymphedema.

Regarding Claim 45, Witte et al disclose the method of claim 1, wherein the wildtype VEGFR-3 allele comprises the VEGFR-3 coding sequence set forth in SEQ ID NO: 1.

Regarding Claim 46, Witte et al disclose the method of claim 7, wherein the wildtype VEGFR-3 allele comprises the VEGFR-3 coding sequence set forth in SEQ ID NO: 1.

Regarding Claim 47, Witte et al disclose the method of claim 38, wherein the wildtype VEGFR-3 allele comprises the VEGFR-3 coding sequence set forth in SEQ ID NO: 1.

Allowable Subject Matter

11. The following claim has been drafted by the examiner and is considered to distinguish patentably over the art of record in this application:

A method [of assaying] for determining an increased risk of developing hereditary lymphedema, comprising assaying nucleic acid of a human subject for a mutation that alters the encoded amino acid sequence of at least one VEGFR-3 allele of the human subject and reduces ligand-mediated signaling of the VEGFR-3 polypeptide encoded by the allele, when compared to VEGFR-3 encoded by a wild-type human VEGFR-3 allele; wherein the mutation is selected from (1) a missence mutation at nucleotide 3360 of SEQ ID NO: 1, causing a proline to leucine change at residue 1 1 14 in SEQ ID NO: 2,. (2) a missense mutation at nucleotide 2588 of SEQ ID NO: 1, causing a glycine to arginine change at residue 857 in SEQ ID NO: 2, (3) a missense mutation at nucleotide 3 141 of SEQ ID NO: 1, causing an

arginine to proline change at residue 1041 in SEQ ID NO: 2; (4) a missence mutation at nucleotide 3150 in SEQ ID NO: 1, causing a leucine to proline change at residue 1044 in SEQ ID NO: 2; and (5) a missence mutation at nucleotide 3 164 of SEQ ID NO: 1, causing an aspartic acid to asparagine change at residue 1049 in SEQ ID NO: 2, and [correlating presence or absence of said mutation in the nucleic acid to a risk of developing hereditary lymphedema,] wherein presence of said mutation in the nucleic acid con-elates with an increased risk of developing hereditary lymphedema[, and wherein absence of said mutation in the nucleic acid correlates with no increased risk of developing hereditary lymphedema].

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:30 TO 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
Patent Examiner
Art Unit: 1634
May 15, 2003